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Early Stage Cervical Cancer, Therapy for Reproductive Health and Quality Survival

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Abstract: Cervical cancer, one of the leading causes of cancer deaths, seventh in frequency amongst all the cancers, third most common cancer in women, after breast and colorectal cancers, accounts for 9% of all cancers in women and 4% of cancers in men and women put together. As cervical cancer is being reported in young women, so preservation of reproductive health and survival with quality has become more important during cervical cancer therapy. For quality survival, reproductive health preservation inspite of cancer, early diagnosis and appropriate therapy are essential. Purpose of this article is to share so that others also look into various issues and we try to do the best for prevention of cervical cancer and provide best therapy so that women have survival with quality and reproductive health is preserved, specially in young women. Review of literature was done and self experiences have been added.

Keywords: Cervical cancer, early stage, quantity life, reproductive health, therapy.

BACKGROUND

Cervical cancer is the seventh in frequency amongst all the cancers, third most common cancer after the breast and colorectal cancers, one of the leading causes of cancer deaths among women, specially in developing countries, including India. It accounts for 9% of all cancers in women, 4% of cancers in men and women put together. It is estimated that 530,000 new cases of cervical cancer must have been diagnosed in 2008 [1 - 3]. Worldwide, cervical cancer causes around 275,000 deaths per year, 80% in the countries with limited resources [4]. Though it is a preventable cancer, but continues to be a major cause of cancer related deaths globally. However if it is detected in early stage, death can be prevented, quality life is possible and even reproductive health can be preserved by appropriate therapy. Population-based studies from developed countries have shown marked socioeconomic gradients in the incidence and mortality due to cervical cancer. Women from lower socioeconomic strata have 2-3 fold higher risk to have cervical cancer than their affluent counterparts [5 - 10]. The difference is mainly because of the availability and utility of screening programs but it could also be related to other causes including diet. Most of the cases of the cervical cancer are because of infection with the human papilloma virus (HPV) and experts believe that a diet high in antioxidants, carotenoids, flavonoids, and folate found in fruits and vegetables can help the body fight HPV and also prevent conversion of cervical cells into cancerous cells by HPV. A study revealed that women who had high levels of certain chemical compounds indicating diet rich in fruits and vegetables were able to clear their HPV faster than their peers, reducing the risk of cancer [11]. It is number one cancer in women of East African and South Asian countries in terms of incidence as well as mortality [12]. More than eight out of ten (86%) cases and 88% deaths due to cervical cancer occur in developing countries [3]. It is our experience that in a nearby province where diet is different, disease seems to occur more often in young women and seems to grow faster as young women report with advanced cancer compared to women of the province from where article is being written. Around 20% global cervical cancer cases are

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from India [13]. However inspite of cancer, early diagnosis and appropriate management help in quality survival and preservation of reproduction health. Present article is based on review of the literature, experiences added for sharing and thought provoking.

Diagnosis

Many women who have cervical cancer report with vaginal discharge, with or without bleeding. This is sometimes preceded by postcoital bleeding. However there may not be noticeable symptoms or signs in early stages of cervical cancer. Unfortunately, cervical biopsy, the gold standard for diagnosis, is quite often not performed and the diagnosis is made after the woman undergoes simple hysterectomy for chronic vaginal discharge, creating many problems in further management. We get many such cases at this rural referral institute in eastern Maharashtra of India. It is essential that health professionals are made aware and they take appropriate action.

Improved imaging investigations such as high-resolution Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET), if done are likely to reveal extrauterine disease which is clinically not obvious. These investigative modalities are not used for staging in this part of the world because of the cost involved. Also these investigations do not detect micrometastasis which affect prognosis. Development of the nanotechnology based research in imaging technology is likely to help in the diagnosis of micrometastasis like the new Nanotechnology-Based Multiplexed Bioassay Platform for Diagnostic Applications project (NANO-MUBIOP) [14]. Nanotechnology might become one of the most promising technologies for the treatment of various cancers by creating drugs which will directly attack the cancer cells without damaging the other tissues. The treatment which has been tested in animal models, consists of a nanostructured composition encapsulating a protein called interleukin-2 (IL-2), lethal to cancer cells and a woman immunosuppressed by the disease produces less interleukin so the use of the nanoparticle is going to be very beneficial [15].

As of now, in this region the diagnosis is by cervical biopsy and staging is mostly clinical, sometimes by examination under anaesthesia. Cervical cancer is more often seen in low resource regions where it may not be possible to do CT or MRI and PET. So sometimes clinical, intra-operative and postoperative staging are not the same. We did a study and found clinical and intraoperative staging agreement in 72% cases and between clinical and final histopathologic staging 64%, (unpublished). Knowing the extent and grade of cancer, helps in decision about the most appropriate therapy. However sometimes distant metastasis might be present in women with early invasive cancer or microinvasive cancer or even carcinoma *in situ* (stage 0), (disease only in innermost lining, no invasion), cases. Primary disease may be diagnosed while investigating/treating disorders because of metastasis. We had a case where the woman presented with fracture of the tibia. While managing the case it was revealed that she had secondaries of cervical cancer. Earlier the woman had gone to a health facility for vaginal discharge, the lesion on the cervix was diagnosed as cervical erosion clinically and chronic cervicitis on histopathology. So she was reexamined and submitted to repeat cervical biopsy. Re-evaluation turned out to be invasive cervical cancer (unpublished). So it was missed diagnosis. Another case diagnosed as cervical cancer *in situ* on cervical biopsy, when opened for laparotomy for simple hysterectomy (as she was many years beyond menopause and had follow up problems), revealed secondaries in the abdomen. Review of the slides of cervical biopsy was done which revealed micro invasive cancer, little beyond the first diagnosis of *in situ* cancer [16]. So sometimes local early disease could be advanced.

Cases with carcinoma *in situ* or stage 0, IA1 and IA2 with microscopic invasion not more than 3 mm deep, not more than 7 mm wide, more than 3 mm but not more than 5 mm deep, not more than 7 mm wide respectively, IB1 microscopic more than 5 mm deep or more than 7 mm wide or visible disease but 4 cm or less and in stage II A1 beyond the cervix but not to the pelvic wall or to the lower third, can only be called early stage cancers for all practical purposes [17]. In these cases single modality of therapy might be sufficient. Risk in cases of IB2, (larger than 4 centimeters tumour), IIA2 (more than 4 cms with, vaginal involvement), IIB (spread to tissues around the uterus but not pelvic wall) are too advanced to be included in early stage though outcome in these cases is better than real advanced cases stage III and IV.

THERAPY

In addition to health education and screening (either mass or opportunistic) by various modes, Human Papillomavirus (HPV) vaccine is being recommended as a preventive strategy [18]. New research suggests that a single dose of vaccine is enough [19], however controversies about its use, because of various reasons continue. Cervical cancer occurs in poor women who cannot afford the vaccine and those who are being advised to get the vaccine rarely

get cervical cancer and HPV free cancer is also known [20]. For quality disease free survival (DFS), treatment needs to be tailored to the extent of the disease. Since most cervical cancer cases have precancerous stage for years, prevention is possible and needs to be attempted by treating precancerous disease. Preservation of reproductive health is possible if the disease is diagnosed in early stage. It has become essential to work in this direction as younger women are getting the disease and women are postponing their child bearing. Appropriate selection of therapy is critical for the best outcome.

The modality of therapy depends on several factors, age, parity, tumour size, extent of disease, stage, grade, histology, evidence of lymph node involvement, risk factors for complications of surgery/radiation, associated medical disorders, desire of preservation of fertility and patient preference. Sixty-five years of age is cited as the limit for consideration of radical hysterectomy by some researchers [21], however morbidity and survival of older patients comparable to younger women have been reported [22]. It seems prudent to determine whether a surgical approach is appropriate and safe, based on stage, other risk factors independent of chronological age [23]. Three standard therapies are Surgery, Radiation or Chemotherapy used singly or in combination. Surgery, if possible is preferred, as the diseased part/organ is removed from the body, however it has to be safe and must lead to survival with quality. In selected cases of stage IA1, loop electrosurgical excision procedure (LEEP) performed in outpatient may be an acceptable alternative to cold-knife conization. It obviates the risks of general anesthesia needed for cold-knife conization [24, 25], however controversy exists as to the adequacy of LEEP, as a replacement to conization [26, 27]. Also unrecognized invasive disease treated with inadequate ablative therapy may be the most common cause of failure of therapy [28]. Further the use of LEEP in patients having occult invasive cancer might lead to inability of determining the depth of invasion accurately. A study has revealed that lymph-node involvement in these patients is low [29]. For women of postreproductive age who cannot or no longer wish to have children and follow up is a problem, total hysterectomy (vaginal/abdominal) is advocated. If surgery is not possible, internal radiation is advocated [30, 31]. It is the most common modality used in Indian women who complete their child bearing early. There is lack of awareness and also there are other problems like dependence, resources and follow up. Therapeutic strategies need deviations according to the situation. For rural poor women radical decisions are taken even for preinvasive disease. The classical surgical management of stage IA1 with lymphovascular space involvement, IA2, IB1, and IIA1 is radical hysterectomy (RH). Though conception in her own uterus is not possible as of today, ovarian preservation, sexuality, quality survival are possible with the possibility of having her own baby by surrogacy. Radical hysterectomy with node dissection is considered for patients where the depth of tumor invasion is uncertain because of invasive tumor at the margins of the cone taken out for diagnosis. In early stage, pelvic lymph node metastasis is expected in 10-15%, in 17% cases of stage IB and 12-27% in stage IIA. In node negative patients, pelvic lymphadenectomy has low benefits, increases the risk of lymphocyst and lymphedema which affect quality of life [31, 32].

Intraoperative detection of metastasis by Sentinel Lymph Node (SLN) mapping with peritumor injection of radio isotope and blue dye with or without lymphoscintigraphy with a gamma probe has been proposed for identification of node involvement in early cancer. SLN can be subjected to extensive evaluation, immunohistochemistry to detect micrometastasis more accurately and minimize post-operative morbidity by avoiding unnecessary lymphadenectomy. However at present there is no clear evidence to support the use of sentinel node removal in preference to pelvic lymphadenectomy [33]. A combination of internal and external radiation which is usually advocated for IB2, IIA2 and IIB, may sometimes be best therapy, even for early stage cases (IA1, IA2 and IB1). Deep stromal invasion, large tumor size, and lymphovascular invasion are intermediate risk factors and if any of these are identified, adjuvant radiation decreases the risk of recurrence [34]. The selection of either option depends on various factors and expertise available. Radiation or radical hysterectomy with pelvic lymphadenectomy result in cure rates of 85 - 90%. A randomized trial reported an identical 5-years survival and disease-free survival (DFS) after radical hysterectomy and radiation [35]. RH causes damage to the autonomic nerves. Damage depends on radicality of surgery. This might lead to bladder and sexual dysfunction as the nerves are also responsible for the increased vaginal blood flow during sexual arousal [36]. Based on various studies, nerve- sparing radical hysterectomy (NSRH) has been proposed as a means of preserving bladder, sexual function [37 - 42]. In NSRH identification of the bilateral inferior hypogastric and the splanchnic nerves is performed during pelvic lymphadenectomy. Identification of ureters below the level of common iliac vessels along the peritoneum of mesorectum is guided with careful dissection of peritoneum and the ureter followed by identification of the inferior hypogastric nerve 1-2 cm below the ureter. The nerve is dissected towards the uterine artery with simultaneous dissection of the inferior hypogastric nerve away from the uterosacral ligament at the lateral part of cardinal ligament [43].

Cunningham *et al.* [44] have reported that after surgical staging, patients with small volume, para-aortic nodal disease and controllable pelvic disease may be cured with pelvic and para-aortic radiation. Treatment by extended-field radiation in patients with unresected periaortic nodes leads to long-term disease control in low volume (<2 cm) cases [45]. Patients with close vaginal margins (<0.5 cm) may also benefit from pelvic radiation [46]. Hertel *et al.* [47] reported that cases of IB1 stage, with negative lymph nodes and absence of angiolymphovascular space involvement are the ideal candidates for laparoscopically assisted radical vaginal hysterectomy (LARVH). Proper case selection with restriction of the procedure to small tumors is essential even for the short-term surgical benefits of LARVH [48]. Less radical surgery in conjunction with pelvic lymphadenectomy (fertility preserving radical operation) is being advocated. In radical trachelectomy, cervix, upper vagina and surrounding tissue along with pelvic lymph nodes are removed. It is followed by Saline procedure to prevent preterm labour. Abdominal route results in wider parametrial resection than vaginal and also there are lower intra operative and post operative complications. In combined laparoscopic and transvaginal approach the reconstruction includes a strong nonabsorbable suture around the isthmus reattaching the uterine stump with vagina (prophylactic ciralage) and closure of the pouch of Douglas, taking care of not obstructing the uterine orifice. In a study with the mean follow up of 23 months, there were no recurrences [49]. Laparoscopic vaginal radical trachelectomy (LVRT) may be the most appropriate answer to the question of fertility preservation in the management of early stage cervical cancer for some women [50, 51] specially in the affluent world, for women of low resources the situation is very different because of problems of accurate staging and follow up. In invasive cancers simple hysterectomy has as high as 60 % risk of recurrence [52]. When invasive cervical cancer is detected after simple hysterectomy, further treatment is either radiotherapy or radical parametrial resection, vaginal cuff removal and pelvic lymphadenectomy. Robotic radical parametrectomy with bilateral pelvic lymphadenectomy is also believed to be feasible and safe. It can be performed with an acceptable complication rate [49]. Geisler *et al.* [53] reported that robotic radical hysterectomy (RRH) with pelvic lymphadenectomy is a promising new surgical technique. It has acceptable blood loss, operating time, clean parametrial margins, appropriate nodal yield and shorter hospital stay. Intra-operative and post-operative complications are comparable to open RH [54 - 56], but long-term outcome needs to be researched. Magrina *et al.* [57] reported operating times for RRH and RH through laparotomy similar, but significantly shorter compared to laparoscopic surgery. Blood loss and hospital stay are similar for laparoscopic and robotic surgery but significantly less compared to laparotomy. Sert [58] reported that Robotic-assisted laparoscopic radical hysterectomy in early stage cervical cancer has better results than total LRH but Kruijdenberg *et al.* [59] have reported that Robot assisted and total LRH are equally adequate and feasible. Research needs to continue.

Radiotherapy/Chemotherapy

Radiotherapy, (external and internal) is time tested therapy in all stages of cervical cancer, however in early stage radiation is reserved for women who are not surgical candidates. In early stage radiotherapy with or without chemotherapy is used only when surgery is not possible because of medical problems or because of patients choice or lack of expertise. Common side-effects of radiotherapy are of, fatigue, bowel, bladder dysfunction and skin problems which can be controlled with diet modification, exercises, oral rehydration and symptomatic therapy, even natural [60 - 62]. Recent reports revealed that radiation therapy for cervical cancer increases risk for colorectal cancers. Young women treated with radiation for cervical cancer should begin colorectal cancer screening earlier than traditionally recommended [63]. When chemotherapy is used, with radiotherapy for better efficacy of the radiotherapy to improve progression free survival, the drug is cisplatin, singly or in combination with 5 fluorouracil. It reduces local and distant recurrences also. The role of radiosensitizing chemotherapy in IA2 and IB1 lesions is untested and is likely to be of only marginal benefit since the cure rates with radiation alone exceed or approach 90% [64]. Also research through nanotechnology is being done for targeted action [15, 65]. Jabir *et al.* [65] and Rotman *et al.* [66] report that the addition of concurrent cisplatin-based CT to RT significantly improves progression and overall survival for high-risk early stage patients who undergo radical hysterectomy and pelvic lymphanectomy. Toxic effects are greater with para-aortic radiation than with pelvic radiation alone but are mostly with prior abdominopelvic surgery. Although low-dose rate (LDR) brachytherapy with cesium Cs 137, has been the traditional approach. The use of high-dose rate, brachytherapy with iridium (Ir 192), is rapidly increasing, as it eliminates radiation exposure to medical personnel with a shorter treatment time and patient convenience.

Radiation in the range of 50 Gy administered for 5 weeks with cisplatin with or without fluorouracil (5-FU) should be considered in cases with high risk of recurrence including those with positive pelvic nodes, positive surgical margins, local micrometastasis [67].

COMPLICATIONS

Surgery is notoriously prone for postoperative complications such as urinary tract fistula, thromboembolism, lymphocyst, lymphoedema, and bladder dysfunction [39, 40]. Intraoperative and immediate post-operative complications of radical hysterectomy include blood loss, uretero-vaginal fistula (1- 2%), vesico-vaginal fistula (<1%), pulmonary embolism (1- 2%), small bowel obstruction (1- 2%) and others like fever, deep vein thrombosis, pulmonary embolism, pelvic cellulitis, urinary tract infection (25 -50 %). In the recent past, Trimbos *et al.* [43] have reported post operative mortality of <1% but high morbidity, urinary tract infection 42%, deep venous thrombosis 3% and fistula 2%. Subacute complications include constipation, lymphocyst formation and lower extremities edema. Postoperative colonic stasis might persist for days [68]. Patients who undergo extraperitoneal lymph node removal have less bowel complications than those with transperitoneal route [45, 69 - 73]. Postoperative radiotherapy results in a significant deterioration of these functions. In high-risk, morbidly obese patients the safety of panniculectomy has been reported as a technical advantage and is achieved by improved operative exposure [74].

Disruption of autonomic fibres of the bladder during operation of the pelvic viscera is associated with significant bladder, anorectal, urinary and sexual dysfunction, but seems to be inevitable [75, 76]. Functional disorders of the lower urinary tract are the most common long-term complications (8-80%) due to partial interruption of the autonomic fibers innervating the bladder during resection of anterior, lateral and posterior parametrium and vaginal cuff leading to sensory loss, storage and voiding dysfunction and incontinence [77, 78]. Partial or complete denervation of the urinary tract results in collection in bladder and urethral dysfunction with negative impact on quality of life [79, 80]. However, research reveals that the size of lateral parametrium measured on giant sections does not differ among these cases. Reports reveal that the length of vagina removed is significantly longer in patients with detrusor dysfunction than in patients with normal diagnosis or genuine stress incontinence [81, 82]. Brooks *et al.* [83] reported that radical hysterectomy does not appear to be associated with more long-term bladder or anorectal dysfunction than simple hysterectomy. Severe anorectal dysfunction is uncommon. Zullo *et al.* [81] report that the pathophysiology of these changes is controversial. Ran *et al.* [82] reported that the retention of urine after radical hysterectomy is not related to loss of blood volume, parity and menopause.

PROGNOSIS

Many factors influence quality survival and reproductive health in early stage cancer, general condition, age, type, stage, response to treatment. Whether advances in diagnostic tools and therapeutic methods improve the overall prognosis of patients and recurrence is debatable but with appropriate treatment in early stages, cure rates go up to 90-100% as reported by Lim *et al.* [84]. Prognosis is affected by undiagnosed parametrial disease, metastasis in pelvic lymph nodes, and positive surgical margins. Involvement of regional lymph nodes is one of the most reliable prognostic factor [85, 86]. Actually node histopathology is considered to be the most important predictor after FIGO staging [87 - 89]. Rose *et al.* [73] reported that the risk of death from cervical cancer has decreased by 30-50% with use of concurrent chemoradiation.

Unfortunately some women with early disease do badly with conventional approaches [85] for reasons not very well understood. Over expression of genes seems to predict the prognosis, investigations which go beyond the reach of those who mostly suffer from this cancer. All said, most patients with early stage cervical cancer can be cured or their disease can be controlled for a period of time which varies from months to years with quality survival. If the disease recurs, the treatment depends upon the stage, past therapy and the condition of the patient. Optimal treatment for recurrent disease is still a debate. Most recurrences occur within 5 years [90], but recurrences beyond 5 years of radiation have been described [91]. Patients with early disease who undergo appropriate treatment have recurrence risk of 10-15%, mostly isolated in pelvic cavity [92]. Fatemeh *et al.* [93] report mean interval of recurrence as 2.75 + 1.5 years after the initial treatment. Earlier Comerci *et al.* [94] reported recurrence in 7.6 % for stages I and II combined, Yamazawa *et al.* [95] report 25 % recurrence in all stages combined, 35.7% in II. We still need to know the factors, which will allow the selection of patients with clinical early disease, who would benefit from more aggressive multimodality regimens from the outset. Factors which affect the final outcome and survival continue to be a dilemma. DFS correlates strongly with depth of tumor invasion, tumor size and capillary-lymphatic space invasion [96].

Dyun *et al.* [97] report average DFS of 18 months, close to findings of recent report of Ohara *et al.* [92]. Lim *et al.* [84] also reported an average DFS of 17.6 months but earlier Mahe *et al.* [98] reported an average DFS, 70 months. Hertel *et al.* [47] report that for recurrence-free survival, tumor stage, lymph node status, and combined involvement of lymphovascular and angiovascular space are independent prognostic factors. DFS may not be significantly different for

age, disease status of the surgical margins, tumor description, quadrant involved with tumor, uterine extension, and keratinizing status of tumor cells. Clinical tumor size, and depth of tumor invasion are independent prognostic factors [99]. Final outcomes include, treatment related morbidity, pelvic floor function, patterns of recurrence, quality of life overall survival, costs and cost effectiveness [100, 101].

CHALLENGES

Unfortunately very few women report at operable stage in part of the world where cervical cancer is common [16, 102, 103] and compliance during therapy and after therapy is low [16]. Further aggressive disease is being detected in younger women (25- 40 years) and old peak of occurrence of disease at 50-55 years has been replaced by plateau between 35-55 years [104, 105]. Recent trends show a resurgence (4- 6 % of cancer in women) of disease in developed countries [106]. Since cervical cancer is mostly preceded by a long phase of precursor lesion, cellular atypia, various grades of CIN before progression to invasive cancer [107 - 112], prevention is the key. Developing countries including India are failing. Presently there are no available methods to differentiate CIN lesions that will progress to cancer from those that will not progress, though attempts are being made to identify factors which can help in prediction, as research continues. Based on the existing knowledge, UICC supported by multiple partners is spearheading the Cervical Cancer Initiative (CCI) to significantly reduce the incidence and mortality of women dying from the disease through targeted and resourced interventions [113].

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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